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HIS GRACIOUS MAJESTY.

We offer our tribute of respect and affection to the memory of a man whose princely attributes made him beloved by peoples of many races and creeds, and of all stations in life, in a day when loyalty to a royal house has ceased to be a social requirement, and has even been relegated to the limbo of other medieval virtues. It was the man who adorned the office and challenged loyalty with affection. This he did by the quality of his personality which, in spite of his official prominence, has not been consciously recognized in all its greatness by most of us until now. The focus of our political thought has been on the powers behind the throne, and not so much on the ceaseless activity of the so-called "figure-head." Perhaps the common man has realized little of the part played by the king in shaping the policy of empire —not in the role of a dictator of decrees, but as a skilled diplomat, the wise father of an adult independent family. Self-interest, which conceivably might be served by such activity, is not compatible with the disregard of his own physical welfare and safety which he exhibited on more than one occasion. All maudlin patriotism aside, the sentiment of the peoples of the empire, from his confidantes to the natives of the colonies, is that he truly loved his people.

EDITORIAL

PHILOSOPHER OR TECHNICIAN?

One has frequently heard the charge laid at the door of physicians and medical students, of narrowness of interest. In spite of the oustanding representatives of the profession whose lives and activities belie such a charge, one feels obliged to admit its truth as applied to a considerable number of the profession. The heavy demands made on the doctor's time perhaps excuse him from extensive excursions into metaphysics but the nature of his work brings him closer to the fundamental forces of the universe than that of any other profession or calling.

If philosophy may be simply interpreted as the attempt to unify knowledge or to correlate the facts of experience, it is the natural pursuit of the physician who seeks a complete picture of Man in his environment. No branch of human knowledge is without interest. The development of the universe, the advent of life, the history of man including anthropology, ethnology, political, economic and religious history, and all other studies which converge on the ordinary man of the present in his environmental setting, may be of immense value in achieving a clear understanding of the main subject of the physician's study—an organism moulded by and reacting to an infinitude of forces.

The physician is almost too busy to launch himself into a study of the fundamentals of a philosophic system. The curriculum of his undergraduate course contained most of these fundamentals, but at the end of six years many of us find that our knowledge consists of odd bits of information that curiously stick in our minds rather than any comprehensive system of ideas. Such has been our intellectual inertia or our lack of interest that we have not formed a pattern of the facts which have been presented and therefore only remember those things which through repetition and emphasis it is impossible for us to forget.

The philosophic attitude is both self-perpetuating and self-stimulating. The structure of thought must first be built of a limited number of facts. Hence many gaps exist which send the builder in search of facts to fill them; the structure is extended with still more gaps, and so on *in aeternum*. A hopeless task, you say, to build a structure which can never be completed. It is a perfect recipe for the treatment of boredom and the maintenance of interest. Moreover, the very semblance of order in such a system makes it infinitely more useful and satisfying than a collection of facts or even of numbers of minor systems. While the physician must be an expert technician with systems of thought and action suited to various conditions, it is hoped that many will also be philosophers, seeing each man as a type of Man in his universal setting.

The Faculty of Medicine has been signally honoured by the invitations which two of its members have recently received to lecture in the United States. Dean Fitzgerald is to give the Herzstein lectures in San Francisco on March 2, 3 and 4. He will be the fifth of a very distinguished succession. His predecessors in this lectureship have been Professors Orbelli of Leningrad. Singer of London, Shaffer of St. Louis and Evans of California.

Professor Best is to inaugurate a new visiting lectureship in Physiology at Yale University. He will spend the month of March in New Haven and will give a series of lectures on various aspects of physiology.

DR. THOMAS McCRAE --- A COMMENTARY*

By NORMAN B. GWYN, M.B., F.R.C.T. (C.)

By the death of a few months ago of Dr. Thomas McCrae, the medical profession of the English speaking countries lost an outstanding member of their fellowship, one, who, from a long association with a great master, as well as by reason of his own splendid qualities, seemed chosen as the disciple to carry on with the master's work. As Osler preached, McCrae practised, and their intimacy was such that any commentary on the life and progress of the pupil leads inevitably to a greater appreciation of the wisdom of the teacher.

Sir William Osler's move to the chair of Medicine at Johns Hopkin's, was followed by a long procession, from Canada, of men eager to take up work under the guidance of that remarkable personality who had so completely upset old standards of medical thought and teaching, and who, by his attraction of followers from far and near was to exert a world-wide influence on the teaching of medicine. as well as to promote to an unusual degree the spirit of international relationships.

Among the many from Toronto well trained in the sciences by his association with Ramsay Wright, Bensley and A. B. MacCallum, well taught in medicine by J. E. Graham and the late Alexander McPhedran, well set in his life's work by residence in the old Toronto General Hospital, was T. McCrae, son of David McCrae of Guelph and brother of the loveable "Jack" whose "Flander's Fields" still plays on the heart strings of a troubled world. Essentially different from the spontaneous and sunny companion of his earlier days, "T. McCrae" was yet to make on the corridors of medicine, an impression no less clearly outlined than that made by his versatile and brilliant brother on the stage of art and literature, for as a teacher, and as a contributor to the medical sciences, Thomas acquired world-wide renown.

A story of success in life and accomplishments, such as is implied in the last few words of the preceeding paragraph carries with it in most instances, the theme of the proper conjunction of the man and the opportunity. In the history of McCrae's progress in medicine and in his academic career this theme has never better been exemplified. Influenced by Graham, formerly professor of medicine at Toronto, who had early been associated with Osler, stimulated no doubt by enthusiastic reports from Thomas Cullen and L. F. Barker who had already gone to spy out the land, urged on, as he has often related by having put before him the publications from the rapidly progressing Baltimore clinic, McCrae arrived at Johns Hopkin's in 1897 and there at once began that intellectual and personal intimacy, with Osler, which, with his own qualities and character, was to fit him for an exalted position in his chosen career—the teaching and the practice of medicine.

McCrae's meeting with Osler coincided most fortunately with the fulfilment of the latter's ambition, namely, that of being at the head of a great teaching school, for up to the time of Osler's going to the Johns Hopkin's Hospital and medical school, he had never occupied the position of chief-of-staff or of head of a medical department. His ability as a director of a great clinic was as yet unproven, and

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* For those students in the lower years, to whom the name of Thomas McCrae may not be familiar, a short biography is printed on page 116.

the propriety of the ideas put forward in his clinic as regards the proper teaching of medicine was by no means undebated, was in fact, in many quarters openly derided; the century-old tradition which bestowed professorships upon the busiest general practitioner, though rudely shaken by the importation of the revolutionary young mind from McGill, still slumbered in the directors' chairs of the governing bodies in every American school.

In 1897, however, the Johns Hopkins' school began to send forth its first graduates in medicine, graduates whose entry to the school had required the production of a degree in the sciences, graduates whose standing, even before the end of their medical studies, at once convinced the medical world that in Baltimore, medicine was being taught in new and improved ways, and that in the teaching thereof, what might be called "Osler ideas and ideals," were much to the fore. As a centre of medical education, Johns Hopkins seemed to have assumed, in a few short years a generally recognized leadership, and the success of the plans promoted by President Gilman and furthered by Osler and his associates was assured.

In the training of these carefully selected classes of students, McCrae was to play a prominent part, a part in which his solid scientific background was combined with the love of teaching and with an unusual power of observation and of accurate deduction while at the same time his capability as physician in the medical wards was such, that his usefulness in the furthering of Osler's many plans for the improving of hospital services and clinical teaching was soon apparent. Less brilliant, perhaps, than other assistants in the direction of pure research, his ability to put the essentials of diagnosis and clinical instruction before the eager student, led quickly to the recognition of the fact that in the person of McCrae, Johns Hopkins' University had acquired an instructor of outstanding worth, one who could be relied upon to assist in the maintaining of the high standard of teaching set by the organizers of the medical school.

Ever quick to recognize efficiency in associates and subordinates, Osler soon began to draw into the meshes of his many activities, the quiet, keen, hard-working Scotch-Canadian whose orderly methods of thought and action went far in the straightening out of administrative details as well as pushing their capable possessor steadily forward on the road of research and investigation. In the main business of the day, that of teaching students and post-graduates, or of the careful handling of the pilgrims from every corner of the earth, to whom Johns Hopkins' Hospital had become a Mecca, Osler had now as assistant, one cast in his own mold, one, who in addition to conforming readily with the routine of hospital and school, could find time to "collect, collate and report," a combination of activities which Osler mas wont to impress upon his favorite associates and students, as something essential to their ultimate success if the teaching of medicine was their goal.

Under such circumstances, and knowing the Osler method of helping the younger man forward by ever increasing his responsibility, it was inevitable that when the scheme for the monumental publication, "The Osler System of Medicine" was put forward, the services of McCrae should be impounded in the editing thereof, and that later in his career, one should see him co-editor with Osler in the latter's greatest work, "The Principles and Practive of Medicine." As might be expected, after such successful associations, the editing and revising of both the "Practice" and the "System" fell eventually upon McCrae's shoulders and a glance at the bookcases of the professon tells a ready observer that "McCrae" has become a household word wherever medicine is practised or preached.

Quite apart, however, from the hon-

our and credit acquired by his association with Osler in his great publications, McCrae was himself becoming a writer and contributor in many and varied subjects, one who will ever be remembered as applying a keenly analytical mind to the investigation of many problems more or less hidden in the cob-webby corners of superficial probing and traditional neglect, and as bringing forward for the inspection of student or reader some one of these problems cleaned, refurnished and straightened out In this direction, the resemblance of his methods to those of his great teacher and associate is striking, for in Osler's career in medicine, the wish to tidy up a littered corner of fancies and refurnish it with solid facts was early most apparent, and in the expositions of both master and pupil the replacing of voluminous unsubstantiated theory by some readily appreciated demonstration is always in evidence.

Fifteen years of such application in Baltimore, closely in touch with those, who in their own spheres, were freely given title as the possessors of the best minds in the profession, fifteen years of teaching, of contributing, and of consulting and associating with the profession of the East and of Canada, had, fitted McCrae to an unusual degree, for a call which was sure to come to one of his accomplishments, a call which should in turn give him a directorship of some great medical clinic, and, in 1912, came the wished for opportunity in the invitation from Philadelphia to assume charge of the medical services in the celebrated old Jefferson Hospital and to direct the teaching in the medical department of the Jefferson school.

The medical atmosphere which McCrae found in the Philadelphia of 1912 differed but little from that of the Philadelphia of 1885, into which Osler had gone from McGill with his own peculiar methods of work and teaching. Strange as it may seem, with the example of Osler's progress before them, the medical men of that great city and district had never really learned the lesson which Osler had tried to teach, namely, that by limiting the number of their outside connections, one might find time to become a real master of the medical art and a leader of medical thought, and that by concentrating one's activities inside the walls of a hospital one could see in a few hours or days more than the busiest general practitioner would have time to look at in weeks or months. Whether after thirty years the lack was of men, of methods, or possibly of means, is beside the question. The fact remains that after these thirty years, Osler's methods now so much in evidence in Baltimore and wherever his students might have settled, had not been generally adopted in Philadelphia, and McCrae, following closely in his master's footsteps, appeared to the busy practitioners of the city of his adoption, a no less unusual character than Osler himself.

Interesting, again as the statement may seem, McCrae on arriving in Philadelphia stepped into a position much more certain and established than did Osler when the latter came to that city from Montreal, for while Osler had accepted a junior professorship in a school conducted along the rough and ready lines still prevalent in the year 1885, his pupil stepped into a full professorship, with complete control of a department, organized and equipped to proceed far afield under proper leadership. Within a few months of his arrival, it was clearly evident that the new professor of medicine had ideas and methods, clear-cut and forceful, which added greatly to Jefferson's claim to leadership in the teaching of medicine, as well as pushing quickly forward in his profession their fortunate possessor, who with his quiet efficiency and attractiveness made a direct appeal both to the conservative element of the old Quaker City, and to the many students and associates connected with the school and hospital.

Of his hold with the profession and of his adoption by the Philadelphians into new and pleasing surroundings one may briefly comment that Osler had been easily tempted to leave Philadelphia for Baltimore, after a five year's connection with the University of Pennsylvania, while McCrae within a few years, thanks to the progress of his great and growing clinic, would see little on the horizon which bid fair to offer anything with opportunities equal to those he could grasp in his new associations

Of McCrae's life and activities in Philadelphia, of the honours acquired, the places and positions given him (for he steadfastly refused to seek or to canvass for place or position) this commentary will not speak, suffice it but to say that during his tenure of the chair of medicine at Jefferson his influence was widely felt, his counsel freely sought, and Philadelphia saw its famous, old medical institution firmly re-established as a centre to which were now attracted keen, far-sighted students, who were quick to realize that in the person of their kindly firm instructor, they saw one who having been qualified to absorb much wisdom from a generous source, ever felt it incumbent upon him to share with those who travelled with him on the way.

Thomas McCrae, M.D., D.Sc., F.R.C.P.*

Thomas McCrae, Magee Professor of the Practice of Medicine and Clinical Medicine, Jefferson Medical College, Philadelphia, died on June 30, 1935, aged 64. Dr. McCrae was born in Guelph, Ont., December 16, 1870, the son of the late Col. David C. McCrae, and brother of Lt.-Col. John McCrae, the author of "In Flanders Fields." He received the bachelor of arts degree from the University of Toronto in 1891, where he was a Fellow in Biology from 1892 to 1894, and received the degree of Bachelor of Medicine in 1895 and of Doctor of Medicine in 1903. He studied at the University of Göttingen in Germany in 1899. On returning to America he became Instructor in Medicine at the Johns Hopkins University School of Medicine, Baltimore, and in 1901 was appointed Associate in Medicine and in 1906 Associate Professor of Medicine. In 1912 he went to Philadelphia as Professor of Medicine at Jefferson Medical College, and since that date has been physician to the Jefferson and Pennsylvania hospitals. In 1924 he was Lumleian lecturer at the Royal College of Physicians in London. He was chairman of the Section on Practice of Medicine of the American Medical Association, 1914-1915. From 1916 to 1925 he was secretary of the Association of American Physicians, and in 1930 its president. He was a member of the American Philosophical Society. In 1927 the University of Toronto awarded him the honorary legree of Doctor of Science.

Dr. McCrae was for years associated with the late Sir William Osler, with whom he collaborated in writing a seven volume "System of Medicine," which he later abridged to five volumes, under the name "Modern Medicine," and which he continued to edit after Osler's death. He was also the editor of the eleventh and twelfth editions of Osler's widely known text-book, "The Principles and Practice of Medicine." Dr. McCrae was devoted not only to the practice of medicine, but especially to the teaching of medicine, and in both spheres of work he won world-wide renown.

He married in 1908 Miss Amy Marion Gwyn of Dundas, who survives him. Dr. Norman B. Gwyn, of Toronto, is a brother-in-law.

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* Reprinted from the Canadian Medical Association Journal, 1935, volume 33, page 224.

VIRUS DISEASES OF MAN

F. O. WISHART, M.A., M.D.*

The intensive study devoted to virus diseases in recent years has provided a clearer understanding of their nature. The object of this paper will be to present briefly something of the present conception of virus diseases and to discuss some of the more important of these in the human group, indicating wherein our knowledge is of practical advantage.

The fluctuation in the use and meaning of the term "virus" exemplifies in a broad way the advance of knowledge in this field of medical research. The term "virus" was originally a very vague and inclusive one, taking in all members of the infective or micro-organismal diseases. Later, however, it became customary to qualify the term "virus" with the adjectives "filterable" and "ultramicroscopic" as these properties became attributed to them. The present trend in the light of more exact knowledge of these disease agents is to use the term "virus" alone. It would appear advisable, therefore, to re-examine the criteria which have been accepted in the past as characterizing virus diseases.

Filterability

The term "filterable" as applied to viruses arose from the discovery by Iwanowski (1892), a botanist, that the juice of tobacco plants infected with mosaic disease was still capable of transferring the disease to healthy plants after filtration. This finding was soon extended and found to apply in many animal and human diseases. However, the term has been a confusing one for certain bacteria can be made to pass filters, while a number of virus agents do so only with great difficulty. In a number of diseases believed on good evidence to belong to the virus group, filtration has not been attempted. Filtration is not simply a mechanical process influenced only by the relative size of pores and particles, but is affected also by such factors as electrical charge and the nature of the virus suspension. Because of these facts ,the term "filterable" has gradually fallen into disuse.

Size

The size of many of the viruses has been determined through the use of the ultra-filters perfected by Elford (1929). These filters, or gradocol membranes as they are called, are made of collodion in accurately graded fineness of pore size. The size of the pores of a membrane can be calculated and a value arrived at for any given virus by ascertaining the pore size of the membrane which it just fails to pass. The order of size of some more familiar viruses measured is given in the following table. Measurement is given in millimicrons; a millicron is 1/1000 micron, i.e. 1/1,000,000 millimetre.

		Average size in milimicrons
Bacteria	B. coli	1500
	Staphylococcus	1000
Viruses	Vaccinia	150
	Herpes simplex	125
	Rabies	125
	Rous sarcoma	100
	Fowl plague	75
	Large bacteriophage	60
	Encephalitis (St. Louis)	25
Large Protein Molecule	Haemocyanin	24
Viruses	Yellow fever	22
	Small bacteriophage	10
	Poliomyelitis	10
	Foot-and-mouth disease	10
Protein Molecules	Serum globulin	6.3
	Serum albumin	5.4
	Oxyhaemoglobin	5.6
	Egg albumin	4.3

*Department of Epidemiology and Biometrics, School of Hygiene, University of Toronto.

The determination of the size of many of the viruses by the use of the gradocol membranes has done much to indicate the constancy of size of a given species of virus. In several instances, additional information has been obtained microscropically, several of the largest viruses being visible in dark-ground preparations or stained smears, though imperfectly resolved. The use of ultra-violet light and a system of quartz lenses has allowed the true size of some of them to be estimated photographically. It is evident that the term "ultra-microscopic" is no longer valid for the larger viruses.

Elementary Bodies.—Reference has just been made to the definite formed particles which have been recognized in the lesions of several virus diseases. Examples are vaccinia, smallpox, chickenpox, herpes zoster, fowlpox, ectromelia (a disease of mice) and psittacosis. These bodies might be described as extremely minute cocci and it has become customary to speak of them as "elementary bodies." In the case of vaccinia and variola, they have been secured in pure suspension and their identity as the actual virus established. The following evidence may be adduced in support of this statement. Infectivity goes hand in hand with these bodies. They increase enormously in number in the developing lesions in the animal host and in laboratory culture on living tissue. Specific agglutinins, precipitins and complement-fixing antibodies for the elementary bodies develop in the serum after vaccination. Such serum has also the ability to neutralize the virus and prevent the development of lesions when mixed with it in suitable proportions.

While the identification of certain of the larger viruses along similar lines appears to be a matter largely of overcoming technical difficulties, the possibility of reaching an understanding of the smaller viruses by similar treatment is much more remote.

Inclusion Bodies.—The typical response of tissues to virus action is hypertrophy followed by destruction of cells. In some virus infections, yellow fever for instance, destruction of the cell supervenes so rapidly that hypertrophy is of minor importance, while in others, such as transmissible tumours of animals, hypertrophy is predominant.

A striking feature of most virus infections is the development of characteristic bodies (known as inclusion bodies within the cytoplasm or nuclei of the cells. So characteristic are these bodies that some workers accept them as provisional evidence of the presence of a virus in several diseases where no virus has yet been demonstrated.

In certain virus infections the related type of inclusion body is so characteristic and typical that its appearance is diagnostic of the causal virus, e.g., the Negri body in rabies and the Guarnieri body in vaccinia and variola.

Some of the cytoplasmic inclusions have been definitely shown to consist of clumps of the actual virus particles or "elementary bodies" in a fatty or lipoidal capsule. Still others are regarded as reaction products of the virus and cell. Intranuclear inclusions appear to be of the latter type.

Cultivation.—Viruses differ from bacteria in that they require living cells for their growth and multiplication. So far no one has succeeded in growing these disease agents on artificial media. In the laboratory, therefore, a suitable animal host must be available or preparations of living cells used.

This latter method of cultivation is deserving of special, if brief, mention. Two techniques are usually used. One consists of inoculating the chorio-allantoic membrane of the developing chick embryo (Goodpasture, 1934) and several viruses have been grown successfully in this way The second technique, an in vitro, one employs minced living tissue in a medium of Tyrode's solution and serum (Rivers, 1935).

These methods have been used not only for the propagation of viruses, but as a means of studying cellular reactions and some of the problems of virus immunity. Vaccination with vaccine virus produced by the methods of Rivers and Goodpasture is receiving extensive trial.

While at present this difference in the growth requirements of viruses and bacteria appears to be a very sharp one, it must be accepted with some reservation. Certain bacteria can be grown on artificial media only with great difficulty, and it is possible that some special factor essential for virus growth, apart from living cells, will be discovered.

Immunity.—A generalization which has unfortunately become an axiom concerning virus diseases is that the immunity following an attack is a lasting one. There are, however, certain exceptions to this rule, such as influenza, common cold, herpes simplex and foot-and-mouth disease of cattle. On the other hand, it is well known that in a number of bacterial infections such as scarlet and typhoid fevers, in general, the resultant immunity is a lasting one. The view which has arisen from this generalization, that virus immunity is of an entirely different order from that of bacterial origin, is probably unfortunate. Many points of resemblance are now recognized in respect of active and passive immunity, carrier state and subclinical infection and immunization. Much of the epidemiology of some virus diseases such as poliomyelitis, is explained on the basis of these last mentioned factors. Thus in poliomyelitis, one is familiar with the comparatively low attack rate and the decreasing susceptibility with increasing age. Investigation has shown the widespread existence of specific antibodies in the blood of so-called normal people, and it is therefore assumed that their immunity is the result of infection with the virus, but of a mild or subclinical variety. Carriers probably form the reservoir of infection as their existence has been demonstrated in this condition.

The nature or importance of so-called tissue immunity is difficult to appraise and nothing can be said with certainty about it. However, various humoral antibodies—agglutinins, precipitins, complement-fixing and neutralizing antibodies—have been demonstrated in a number of virus diseases. Diagnostic tests are based on the development of these antibodies in immune serum and the prophylactic and therapeutic value of a serum appears to be dependent on its neutralizing antibody content. In this regard, it must be emphasized that early administration of immune serum for either prophylactic or therapeutic purposes is essential. It has already been pointed out that viruses multiply in or on living cells and once this parasitism has been established (and this occurs extremely rapidly), serum is without avail. In other words, serum must be there to meet and limit the spread of the infection in the body. This important consideration is well illustrated in several neurotropic virus diseases. An example is louping-ill in which the virus has been found in various parts of the central nervous system several days before the onset of symptoms. Once this localization has occurred, the course of the infection in the cells involved is unaffected by the administration of serum. In virus diseases in general, serum administration at the time of onset of the earliest symptoms is too late.

Indentification of a Virus.

Certain conditions should be satisfied before regarding a disease as due to a virus. It must be demonstrated that the infective agent is smaller than known bacteria and is non-cultivable on lifeless media. In most cases, filtration is possible under certain conditions and filtrates of the infected tissues, bacteriologically sterile, must be capable of transmitting the disease to animals. Not only must transmission be

possible, but transmission in series in such a way that definite multiplication of the infective agent is demonstrated.

The pathological and clinical picture produced in the susceptible animal does not resemble the human disease in all instances. One example is the trivial condition of herpes simplex which, in the rabbit, may develop a striking neurotropism, i.e., an affinity for cells of the central nervous system. In spite of such discrepancies in the human and experimental disease pictures, the virus may be recognized by neutralization of its disease-inciting properties by convalescent serum from human cases.

In still other instances, such as varicella and herpes zoster, the infective agent is host-specific and investigation is hampered by the lack of an experimental animal. An appraisal of all the available data may nevertheless suffice to strongly suggest virus aetiology. Complete proof of membership in the virus group is still lacking in many cases.

Classification.

In view of the constantly changing picture of virus diseases, no satisfactory attempt at classification can yet be attempted. Many classifications have been based on tissue affinity, giving rise to the terms viscerotropic, neurotropic, and dermatropic viruses or combinations of these. Since some viruses may have their tissue affinity altered at will in the laboratory (e.g., yellow fever, viscerotropic in man but capable of being converted into a neurotropic virus for the mouse), such a classification has obvious advantages.

For the purpose of discussion, an arbitrary classification which has something to recommend it, is employed by Fairbrother (1934) in his excellent text, "Handbook of Filterable Viruses." This classification is based on host specificity, in other words, in order of the completeness of evidence of a virus agency. Only a few of the more important and familiar virus diseases will be dealt with in this paper and these will be taken up according to this latter arrangement.

Vaccinia and Variola.

The viruses of vaccinia and variola have already been referred to under "elementary bodies." These minute forms, present in great numbers in vaccinia and variola lesions, were first described by Paschen (1906) and hence are often referred to as "Paschen bodies." They are among the largest viruses known, with a diameter of 150 millimicrons (see table I). Growth by means of tissue culture methods has been successful and at the present time "vaccine" produced in this way is receiving extensive trial.

The close immunological relation of these two viruses is shown by the fact that vaccine virus will confer complete immunity against smallpox. Other serological relationships are demonstrable in the test-tube. Two distinct antigens are shared by both viruses and may be demonstrated by means of agglutination, precipitation and complement-fixation tests. The precipitation and particularly the complement-fixation reaction are of real value where the differential diagnosis between mild or modified smallpox and chickenpox is in doubt. Extracts of vesicle fluid or of crusts from patients are tested for complement-fixing ability by means of serum from rabbits hyperimmunized with vaccinia. The reaction is specific and highly sensitive.

Poliomyelitis.

Man appears to be the only natural host for poliomyelitis and so far monkeys have proved the only susceptible laboratory animal. Even in monkeys, transmission has been successful in not more than fifty per cent. of attempts. Once established, the virus may become very virulent for monkeys and extensive studies have been made of infectivity, active and passive immunity and serum therapy.

The virus is extremely small (see

page 117) and passes readily through bacterial filters. Experimental work appears to show that the virus confines its attack to nerve tissue. Natural infection probably takes place by way of the upper respiratory tract. Implanted on the nasal mucosa, the virus comes in contact with the olfactory nerve endings which are invaded and from this point on, spread is by way of neural axons until the anterior horn cells are reached. The varions early symptoms of the disease are explained on the basis of the passage of the virus through the different brain areas. Progress of the virus along definite nerve tracts from the olfactory bulb to the anterior horn cells has been established in the experimental disease in the monkey. However, in the naturally occurring infection in man, it is not yet known whether the virus is entirely confined to the nervous tissue, though the early signs and symptoms can apparently be adequately explained on this basis (Faber, 1933).

Convalescent as well as adult serum has had very extensive trial as a therapeutic agent in poliomyelitis and there is no sound statistical evidence of its value even when given in the preparalytic stage. The reason for the limited value of serum therapy may be explained by the fact that there is a latent period, perhaps lasting several days, between the invasion of a neuron and the development of signs and symptoms referable to this invasion. On the other hand, the extent to which an effective neutralizing serum may limit the spread of the virus downwards in the central nervous system from one neuron to another by providing a barrier at the synapse is not known. In view of this possible effect in some cases, serum should be administered intramuscularly or intravenously, but never intrathecally.

Serum has been used prophylactically but in this connection it should be borne in mind that the duration of such passive immunity is only about three weeks.

At the present time, no safe or effective vaccine against poliomyelitis has been developed (Leake, 1936).

Measles.

Studies on the aetiology of measles have shown that susceptible individuals will develop the disease following inoculation of whole blood or Berkefeld filtrates of blood taken from cases at the time of development of the rash. Similar results have been obtained with monkeys, in which animal serial passage of the disease has been demonstrated. Filtrates of human nasopharyngeal washings taken early in the course of the disease have also proved infectious for monkeys. These findings, together with the unconfirmed and divergent reports on a bacterial agency, appear to place this disease definitely in the virus group.

The character of the disease and its highly infectious nature are too familiar to require comment here. The morbidity and mortality in young age groups are high. Fortunately, convalescent serum as well as adult serum has proved of real value in controlling this disease. Careful studies have established the efficacy of the following prophylactic procedure.

Convalescent measles serum given in 5-10 cc. doses intramuscularly during the first five or six days after exposure will prevent the disease by conferring a passive immunity which lasts three to four weeks, after which the individual is again susceptible. If the serum is given between the sixth and ninth days after exposure, only a mild attack results, but confers active immunity. After this period, serum fails to affect the course of the disease. Pooled normal adult serum is also effective but larger doses are required. in this way, it is necessary to decide when prevention and when modification is desirable. Measles mortality is greatest in children under four or five years of age and in older children in poor health or suffering from some intercurrent infection. These individuals,

therefore, should be given serum as soon after exposure as possible in order to prevent the attack. In all others a modified attack is preferable. This may be secured by delaying serum administration until the sixth to ninth day. By this means, permanent immunity may be acquired without undue risk.

Mumps.

The recent investigations by Johnson and Goodpasture (1934) have definitely confirmed previous experimental evidence supporting a virus aetiology of mumps. These workers injected filtrates of saliva from early cases into the parotid glands of monkeys by way of Stensen's duct. The animals developed the clinical picture of mumps, while controls injected with normal saliva remained well. The disease has also been successfully transmitted from monkey to monkey. Some good results have been reported on the use of convalescent serum prophylactically.

Influenza.

Reasonably certain evidence that a virus plays the primary role in the causation of influenza has been obtransmitted in series in ferrets and mice by the intranasal instillation of filtrates of throat washings obtained from influenza patients. Infection was prevented when convalescent serum was mixed with the filtrates. Various bacteria may be important as secondary invaders, giving rise to complications in the weakened patient. The immunity developed following an attack appears to be a very transitory one.

Common Cold.

Many different organisms have been advanced as the cause of acute coryza, or common cold. Experimental investigation has demonstrated, however, that a virus transferred to chimpanzees and human volunteers by intranasal inoculation of filtered nasopharyngeal washings from cases of coryza will cause the disease. In colds of this type, the virus is to be regarded as the primary invader and any alterations in the bacterial flora of the respiratory passages as sequelae to this invasion. It is not known, however, whether every cold is due primarily to invasion by this type of virus. Immunity following an attack is of comparatively brief duration.

Varicella.

Research studies of chickenpox have been hindered by the lack of a susceptible laboratory animal. Considerable information has, however, been secured. The presence of the infective agent in the vesicular fluid has been demonstrated by dermal inoculation of susceptible children. Such fluid taken under aseptic conditions is bacteriologically sterile and virus activity has therefore been postulated.

Formed particles, very similar in size and appearance to the elementary bodies of vaccinia and smallpox, are present in vesicle fluid of varicella cases. Recently Amies (1933) obtained these bodies in pure suspension by fractional centrifugation and demonstrated their agglutination by convalescent varicella serum. Control tests with normal and antivaccinia serum were negative. Vesicle fluid of herpes zoster has also been shown to contain elementary bodies and cross agglutination obtained with those of varicella and the respective convalescent sera. These facts are in accord with a long suspected relationship between these two disease conditions.

Convalescent varicella serum prevents infection in susceptible individuals but in view of the mild character of the disease, its use has been very limited. Possibly the chief value of such serum would be in infectious disease hospitals and children's hospitals and other institutions where this extremely contagious disease so frequently presents a real problem in cross infection.

SUMMARY.

In this brief review, it has not been possible to deal with all the interesting aspects of virus diseases as they occur in man. Many interesting and important members of the group, such as yellow fever and the encephalitides, have perforce gone unmentioned. Dogmatic pronouncements have been avoided in view of the conflicting ideas and evidence on many points appearing in the literature. The attempt has been rather to present those facts which appear most reasonable and in best accord with the present conception of viruses. It is hoped that the reader will look on this outline of the progress which has been made and of the problems which await attention as a stimulus to further study.

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MEDICAL SOCIETY, UNIVERSITY OF TORONTO

Statement of Receipts and Disbursements

for Period May 16th, 1934, to June 13th, 1935.

RECEIPTS

Cash in Canadian Bank of Commerce May 16th, 1934	$ 596.15
Fees from Bursar	2,542.00
Medical Journal Surplus	23.22
Medical Athletic Association	200.39
	$3,361.76

DISBURSEMENTS

Women's Medical Association	$ 110.00
Medical Athletic Association	1,069.50
John Copp Scholarship	300.00
Medical at Home Committee	227.84
Daffydill Committee	25.86
Joint Executive S.A.C. Torontonensis	50.00
Christmas Donations to Employees	55.00
Bursar University of Toronto, Medical Society Bursary Fund	1,100.00
Sundry Disbursements (see attached list)	373.57
Cash on Hand, Canadian Bank of Commerce, June 13th, 1935	49.99
	$3,361.76

Subject to the fact that we have not verified receipts other than fees from the Bursar and that all disbursements have not in all cases been supported by properly approved vouchers rendered by payees, we report that the above statement represents a proper and true view of the receipts and disbursements of the Medical Society, University of Toronto, for the period May 16th, 1934, to June 13th, 1935.

(Signed) SMITH and SEDDON,
Chartered Accountants.

Sundry Disbursements
May 16th, 1934 to June 13th, 1935

Telephone	$ 27.00
Caretaker—open meetings	6.00
Stamps	3.57
Flowers	7.78
Ballots	22.43
Stationery and placards	22.64
Dance and Banquet tickets	41.30
Office Supplies	1.30
Medical Society Keys	78.52
Shelves and doors	29.88
Travelling expenses	59.40
Photographs	58.75
Audit	15.00
	$ 373.57

RECENT CANCER RESEARCH

A. W. BAGNALL, B.A., '37

Malignancy is a natural disorder and one only too likely to occur in such a structure as the human body. The basic cause of cancer, like the secret of life itself is probably not available to humankind but medicine can study cancer in its evident phases. Since we cannot come to a complete understanding we shall try to discover in what manner the problem is being vestigated.

Three of the more important aspects of Cancer Research will be considered in this paper.

(1) Transplantable tumuors and Immunity.

(2) Induced tumours and plausible theories as to the relationship of cancer.

(3) Genetic Investigations.

Transplantable Tumours

Once it was found that tumours occurred in most. if not all, of the lower animals, a wide field of experimentation was opened. In this transplantation soon came to play a large part.

It was early discovered that animals of the same pure strain as that bearing a tumour accepted transplants of a malignant nature practically without exception. Hybrids of the same species were varyingly wary according to their genetic relationship whereas animals of a similar but different species were persistent in refusal of a tumour graft. It must be remembered however, that grafting of normal tissues is limited in just this same fashion. Biological characters, such as growth rate, tendency to retrogress, etc., are characteristic and a quantity to be known before commencement of an experiment which is to withstand sound criticism.

The important question, relative to transplantation of tumours, is not the success, but the nature of the failures —the immunity. Some animals have a natural genetic immunity, others acquire it by regression, or by successful excision, of certain of the transplantable tumours. Other malignant neoplasms confer immunity under no circumstances. Transplants from one species to another are notoriously futile, even when the animals are so closely related as mouse to rat. It is true that some successes have been reported and substantiated—but these are merely successful acidents in so far as the end-result is concerned. Age proves to be something of a factor for it has been found that a series of young animals is more susceptible to homologous, or even heterologous tumours, than a similar series of older ones, as to the site of transplant. It has been shown that no tissue is more susceptible than any other, with the possible exception of the brain. The search for the site of origin of resistance has met with little success, in spite of numerous experiments on every available tissue. In answer to those experiments tending to point to the Reticulo-endothelial system as the responsible one, it has been shown that there is increased resistance to tumour transplant when the Reticulo-endothelial system is completely plugged with injected dye-stuff. However, this may be explained as a cachetic state and it is known that a young, healthy animal is more susceptible to tumour transplant than an older, undernourished or cachetic animal. This last statement may be construed in two ways, in the first, to bolster the Reticulo-endothelial resistance theory, in the second to argue that the whole subject of transplanting tumours in lower animals is extraneous since the average human case is found in people past their prime or in weakened tissue. Murphy and others claim much from their experments in favor of the lymphocyte and plasma cell being active

agents in resistance. In general, the variance of results from the world's laboratories seems to point to one conclusion only—that, so far, we have not definitely discovered any tissue responsible for immunity.

Investigating from a bacteriologcal aspect, Lumsden and Macrae have consistently claimed demonstration of specific anti-cancer bodies in the serum of rats bearing a regressing Jensen Rat Sarcoma and also in rats which they claim to have been recently immunised against the same tumour by a series of weekly intraperitoneal injections of minced tumour (Jensen Rat Sarcoma). These antibodies are toxic to all types of malignant cell but not to normal tissue and are present only where the body is effectively combating a tumour.

Removal of pituitary hormones, (by hypophysectomy or irradiation of the pituitary) retards the rate of growth of a mammary carcinoma, (Walker carcinoma). Lambret has given a course of insulin treatments previous to tumour inoculation and finds that the tumour grows as normally as in the controls for about ten days, when it suddenly and rapidly regresses and is often completely absorbed. Further in this hormonal series it was found that the crude depressor colloid fraction of normal urine contains a substance (not prolan or kalliknein) capable of breaking down the resistance to tumour inoculation (Carcinoma 256 in rats) and of increasing the rate of tumour growth. Once again, the field is flooded with contradicting results in other experiments as to the influence of hormones on transplanation. However it does seem that the rate of growth of, or susceptibilty of an animal to, a malignant tumour may be consistently varied by tightening or slackening certain known reins.

Before closing this particular section of the subject, it may be important to mention that, although almost invariably it is the transplanted malignant cells alone which develop into the new tumour and acquire stroma, blood vessels, and sometimes even a crude network of nerves from the new host, very occasionally, in a series of transplants the connective tissue element derived from the host becomes increasingly malignant with each transplant so that eventually a pure transplantable sarcoma develops where was before a pure transplantable carcinoma. The explanation has so far been withheld.

This field has been ploughed over time and again. Each time new soil is turned up but seldom any that is more productive.

Induced Tumours.

A little over twenty years ago, Fibigen, in Denmark, accidentally discovered that he could produce, almost at will, gastric epitheliomata in rats by feeding them with nematode-infested cockroaches. In many cases these were truly malignant and metastasized with no nematodes in the secondaries. This method was most cumbersome and thus was soon superseded when two Japanese reported successful production of epitheliomata by painting tar on rabbits' ears over a long period of time. This was the beginning of a most fruitful line of experimentation.

Two distinct trends may be followed—the first is largely an investigation into accupational cancers of tar type from a public health standpoint, and the second is into the chemistry of the carcinogenic tar agents and their relationship to naturally occurring compounds in the body. Much of the newer work may be found here.

Occupational Cancer.—The work of C. C. Twort and R. Lyth has shown (a) that the lower the refractivity of an oil, the lower is its carcinogencity.

(b) A new method of measuring the carcinogencity of a shipment of oil—by intraperitoneal injection of a sample, removal in 48 hours, and examination of the fall of refractive index. The degree of fall is shown to parallel the carcinogenicity of the oil and it is thought to be due to a chemical change,

probably oxidation or reduction rather than a selective absorption.

(c) That a mixture of equal quantities of anhydrous lanolin and olive oil applied to the skin before and after exposure, is of considerable protection against the development of both carcinoma and dermatitis.

(d) Mineral oils and tars rapidly produce dermatitis, slowly produce cancer and the smaller the molecule of a constituent the more it is likely to produce dermatitis instead of cancer. Arguing along the line that the more easily an animal can deal with a foreign substance the more violent will be the reaction, they point out that the dermatitis is a violent reaction to a smaller molecule, while the cancer is a very slow, very massive reaction to a larger molecule.

The term "Induced Tumours," today has become practically synonymous with the production of a tumour of which tar cancer is the prototype. In discussing this, I would like to introduce four distinct aspects:

(1) The production of Cancer by Pure Hydrocarbons.

(2) The Oestrogenic Activity of some Carcinogenic Hydrocarbons.

(3) Metaplastic and Apparent Carcinogenic Activity of Oestrogenic Substances.

(4) Possible Relationship of Natural Sterol Metabolism to Cancer.

Production of Cancer by Pure Hydrocarbons.—Kennaway and Cook are the leaders in this field. By application of the compound in benzene to the intrascapular region of mice twice a week, they produce an epithelioma; by injecting the compound subcutaneously over long periods in a fatty medium, generally lard, they produce a sarcoma. Of tests on a large number of compounds, chiefly tetracylic and pentacyclic aromatic hydrocarbons, they have found that, with only one exception, those showing considerable activity are all derivatives of 1:2 benzanthracene. Of course, this does not mean that all carcinogenic compounds are necessarily related to this, especially since an entirely unrelated compound, while being tested for trypanocidal activity, was recently found to produce a sarcoma. Even straight-chain compounds may soon be shown to have definite carcinogenic activity. However, it is undoubtedly true that at least the major part of the activity found in coal-tar is due to these tetracyclic phenanthrene-ring derivatives. Synthesis of the same compounds has shown them to possess the same activity as when isolated from coal-tar—an important point. It is true that arsenic, aniline substances given off by certain parasites, and long continued regenerative processes give rise to cancer but the metamorphosis is slower and less sure. This serves to show, however, that the change is non-specific requiring only any sufficient means of induction.

The variety of experimentation may perhaps be shown by mentioning that tar epithelioma has an increased incidence after sympathectomy of the region, and also when mice are fed on diets supplemented with liver, but not if the diet supplemented with a preparation of pig stomach mucosa.

Oestrogenic Activity of Carcinogenic Hydrocarbons.—The similarity in chemical structure between the recently analyzed carcinogenic and oestrogenic groups of substances led to the test of carcinogens for oestrogencity. Following on the discovery that some extracts of bituminous material were definitely oestrogenic, Cook and Dodds showed that several of the most active carcinogens were definitely oestrogenic, although by no means all showed such signs of diverse biological nature, however, there seems to be little or no parallelism between oestrogenicity and carcinogenicity in these hydrocarbons structurally related to both series.

Metaplastic and Apparent Carcinogenic Effects of Oestrin.—The following experiments have recently been performed on given strains of mice where

the mammary cancer rate and age incidence is genetically determined and known to be high.

(a) If ovaries are removed at 2 months, mammary cancer incidence falls to zero in all strains.

(b) If ovaries are removed at 3-4 months, falls to zero in majority of strains and approaches zero in the rest.

(c) If ovaries are removed at 8-10 months, incidence is as high as normal.

(d) Weekly injections of oestrin from birth caused an increased incidence of mammary cancer and a lower age incidence in the females of a strain and produced mammary cancer in the male where it would not ordinarily occur at all. This work was done by Lacassague and he points out that in such cases in both sexes the mammary ducts develop early as a rich network which becomes progressively dilated by a secretion analogous to colostrum. The presence of this material and the plugs formed, early sets up an irritation that almost inevitably terminates in cancer. No folliculin was found in this mice colostrum but it was found in human colostrum and in the cyst fluid of a woman with mammary cancer although extracts of the neoplasm itself are negative.

(e) Observation of a high tumour rate strain showed oestrus to be exaggerated in the pre-cancer age when compared to a low tumour-rate strain.

The synthesis of polycystic compounds of both oestrogenic and carcinogenic properties, the presence of oestrin in cancers and in the blood of tumour bearing male mice, and the correlation between the amount of oestrin in the body and the incidence of spontaneous mammary cancer in susceptible strains of mice, suggests some definite connection between epithelial growths and the female sex hormone. Studies of the effect of daily oestrone injection 10 weeks in castrated mice have shown a complete metaplasia of the uterine mucosa to statified squamous epithelium and very recently cancer of the uterus has been reported as a result of such treatment.

Burrows has discovered that prolonged administration of oestrin causes hyperplasia and metaplasia of the prostate in males and that such is the condition of the prostate just before birth in both mice and children but normally this is reversed after the influence of placental oestrin has been removed in delivery. Changes in advanced life in benign enlargement of the human prostate resemble in character and situation those present in mice under the influence of oestrin in newborn babies. Since oestrogenic hormones are present in males, speculation may be indulged in, though carcinoma of the prostate has not yet been produced by oestrin injections.

In connection with breast cancers of the human, be it noted that these occur more frequently in those cases in which a child has not suckled over a definite and adequate period of time i.e. where products of secretion are left to decompose. Now, application of oleic acid to the breast over a period of time will cause epithelial hyperplasia, at best a benign tumour. Chrysene in liquid parafine has however only a shade of the carcinogenic effect of chrysene in solution in oleic acid in which case long application results in the production of an epithelioma which rapidly becomes malignant.

From all this, it is suggested that the chief etiological factor in cancer of the breast is a group of compounds containing the carbon skeleton of phenanthrene, acting with oleic or some other unsaturated fatty acid as a sensitizer. Hence the definite rate of mammary cancer incidence of a strain of mice or (humans) may depend on the inherited characteristics of oestrin metabolism, combined wth circumstances which allow formation of sensisitizer substance. It is also suggested by the results of such experiments that, since metaplasia, at least, of the reproductive organs of both male and female has been definitely related to oestrin,

malignancy itself may supervene after the dynamic qualities of the cell have once so been changed in response to these chemical agents.

Possible Relation of Sterol Metabolism to Cancer—This is a most fertile field for investigation as yet hardly touched. Among compounds found naturally in the human body which are also of the same essential structure as the carcinogenic substance are:

(1) the testicular hormone.
(2) the luteal hormone.
(3) Vitamin D (cholesterol and ergosterol and calciferol).
(4) the bile acids.
(5) (most recently) the embryological evocator substance.

The diverse biological nature of some of these have already been shown —e.g. Vitamin D and its closer relatives (except cholesterol) are oestrogenic; carcinogenic substances are prepared from bile acids and much is transpiring at the moment in connection with evocator substance. The latter is a definite chemical substance capable of causing the ectoderm of the amphibian gastrula to differentiate into neutral tissue. It is present in every cell of the gastrula but active only in the region of the organization centre. Probably several of these govern the differentiation of various cell-types in the embryo, their activity perhaps varying with their concentration. In the adult newt similar fields of differentiation and regeneration are presided over by chemical substances so that undifferentiated tissue transplanted from an entirely different region is made to differentiate into tissue of the type in that new region. At any rate, following the discovery of such substances by Spermann, Waddington and others proceded to elaborate their effects and determined that the chemical constitution of the neural plate evocator of the newt at least, was very similar to that of the carcinogenic hydrocarbons. The latter were also found to evoke neural plate formation in a foreign area of the gastrula when placed in opposition with that area. Cancer tissue is being transferred into embryonic regions where powerful evocator fields are at work and also the influence of carcinogenic agents on regeneration is being investigated with a view to determining the relation between carcinogenic agents and the upset exchange in internal metabolism of a cell which is apparently brought about by them.

Always then we arrive at this same fundamental conception of cell balance in respect to growth energy and we find that various factors may influence such a cell to step up its dynamic qualities or to let them collapse. We are arriving at some ideal of the type of compound which we may call a dynamic stimulant, and Murphy in connection with Rous fowl sarcoma has isolated from normal tssue a factor which diminishes cell growth. The problem is very much alive.

Heredity

Strains susceptible to spontaneous cancer have been bred, but they are only susceptible to lung, liver or stomach cancers but resistant to cancers of other regions. Similarly, immune strains may be obtained.

A difference of opinion sets in when the actual genetic factors are regarded. Miss Slye claims to have established that inheritance of cancer characters is according to Mendelian law and a recessive trait. Lynch has reached the tentative conclusion that it is a semi-dominant trait. The upsetting factor in such experiments is the danger of intercurrent infection causing death before cancer figures are obtained because of the comparatively late cancer age.

Recently, by a rather well-controlled series of experiments, a high lung-tumour-rate-strain has been shown to be highly resistant to induced skin cancer while a low lung-tumour-rate-strain has been shown to be markedly susceptible. The evidence here pointed again to a semi-dominant heredity and moreover, seemed to prove the impos-

sibility of heredity of malignant characteristics being dependent on a single gene.

Whether one may draw analogies for humans from these figures for animals can only be definitely settled by considering at the end of another century the results of application of accurate scientific knowledge of diagnosis, pathology, and gentics to the statistical consideration of cancer in man. In the meantime, however, we must take what is offered and use it as best we can to help us decide the problem.

Statistical studies of cancer the world over show that its incidence in every land is approximately the same. There is a remarkable variation however, in the most prevalent site of the cancer in different lands, e.g. a large number of cancers of the cervix will be balanced by a paucity of cancers of the breast. The incidence of cancer seems equal in the sexes, as well as in the communities and shows no statistical evidence of being a communicable disease. Two rather interesting results have come out of certain surveys.—(1) the incidence of subsequent and apparently unrelated cancer in a cancer recovery is greater than in the general population and (2) the frequency with which cancer occurs simultaneously in two places in the body is considerably greater than was once thought. These two facts point once again to a condition of susceptibility of the body to malignant processes.

So far as we have gone, the evidence is all in favor of the malignant process being a breakdown in the internal metabolic balance of the cell which that cell is prone to undergo by reason of certain characteristics which it has inherited in itself and probably because certain tendencies to dysmetabolism have been inherited by the body as a whole or by some particular system—thus accounting for the selection of certain individuals and the site of the malignant processes in those individuals. The discovery of the Rous sarcoma with its filterable agent has thrown some shadow of doubt on such an hypothesis but J. B. Murphy has offered a very ingenious and plausible reconciliation of the apparent discrepancies. Reference in this connection should be made to the companion article by Mr. Lewis.

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RECENT CANCER RESEARCH—PART 2

By M. D. LEWIS, B.Sc., '36

In Part 1 the contributions of the biochemist, the experimental embryologist, and the geneticist and statistician to our knowledge of cancer were discussed. In this paper some of the other approaches to the problem of malignant growth will be considered.

Tissue Culture

First will be discussed some of the information which the histologist has given us as the result of his study of tissue cultures of normal and malignant cells. The methods used need not be described; all that needs to be made clear is that in a tissue culture the tissue does not merely survive, it actually grows.

Using this method it was early found that a tissue culture of normal cells if properly looked after, could be kept alive indefinitely. Thus one such culture of fibroblasts from a chick's heart has been kept growing since 1911 without any evidence of slowing up or of differentiation into adult fibrous tissue.

The fact that these cells can be made to multiply indefinitely shows that normal cells are potentially immortal, and that these potential powers can become actual in tissue culture where proper nitrogenous food is continuously supplied, and products of metabolism which might hinder growth are continuously removed. But in the body cells do not multiply indefinitely, they stop growing, they differentiate into functioning adult cells, and finally they die. The reason for the difference must lie in the enironment of the cells; the things in the environment that allow cells to grow must be lacking.

These facts about cell growth have been found to apply also to malignant cells. They too can be kept growing indefinitely They soon lose in tissue culture the morphological peculiarities that characterized them when they were part of a tumor. Contrary to common belief they do not grow faster than normal cells of the same type. They do not seem at all "lawless" in ther growth, and in fact they are indistinguishable in appearance from normal cells.

Malignant cells therefore have not any greater inherent growth energy than normal cells, which, as we have seen, can go on growing indefinitely in the presence of a proper environment. Once this viewpoint is accepted we begin to wonder, not why do cells grow, but what it is that stops them from growing; not why do we get tumors, but why are they not much more common. Our problem becomes, not why do certain body cells take on a peculiar lawless neoplastic tendency, but rather what is the nature of the change which must have occurred in the environment of certain body cells to allow them to grow in this unrestrained manner.

The nature of the environmental control over growth and differentiation is not known, but as was indicated in Part 1, the experimental embryologists have recently thrown some light on it. They showed, you remember, that the growth and differentiation of cells is determined by the presence near them of chemical substances similar to the carcinogenic coal-tar derivatives. This suggests that whenever certain body cells begin to grow unrestrainedly to form a cancer, it may be because some of these chemical substances have somehow appeared in their environment.

Cell Metabolism

The physiologists studying the metabolism of the cell have also given us some interesting information. For example, a few years ago Warburg described the phenomenon of aerobic

glycolysis. The simple facts of this phenomenon are these. Cells can utilize glucose for the production of energy in either of two ways. They may oxidise the glucose with the formation of CO_2 and H_2O, a process which is only possible when oxygen is available. This is called respiration. Or they may break down the glucose into lactic acid, liberating energy without the consumption of oxygen. This is called glycolysis. The normal cell, though capable of some glycolysis, gains its energy by respiration, and only resorts to glycolysis during oxygen lack. Warburg's discovery was first, that malignant tissue utilises glucose largely by glycolysis whether oxygen is available or not, and second, that malignant tissue can survive by virtue of glycolysis even in complete oxygen lack, whereas normal tissue cannot.

Warburg's work has been criticised on the ground that this essential difference in cell chemistry between normay and malignant tissues is not a universal rule. However it seems to be quite widely accepted, and quite a great deal of experimental work has been based upon it. For example, the effect of radiation on cell metabolism has been studied, and it has shown that it lowers the respiratory function of cells, normal and malignant, and that this inhibition of oxidative processes reaches its maximum in 48 hours. Aerobic glycolysis, which supplies about 30% of the energy requirement of malignant tissue even in the presence of oxygen, remains however comparatively unaffected by radiation. This seems to indicate that radiation has no selective destructive effect on malignant cells, since if it did, one would expect glycolysis to be inhibited mainly.

Based on these findings there have been attempts to increase the effectiveness of radiating malignant tumors. For instance, Dr. Franks of the Dept. of Medical Research at this University, has made the following suggestion. "Malignant tissue, we know, derives its energy from both oxidation and glycolysis. After radiation, when oxidation is depressed, the tumor is almost entirely dependent upon glycolysis. If now glycolysis could be interfered with, it seems reasonable to suppose that the tumor would be adversely affected." He therefore attempted to inhibit glycolysis by destroying the glycolytic mechanism of the cell with iodo-acetic acid 48 hours after radiation when oxidation was at a minimum. He reports that an appreciable inhibition of the growth of one tumor stran and a slight inhibition of the growth of another resulted. While these results are not conclusive, nor as yet applicable in vivo, they are certainly very interesting and encourage the hope that some way of increasing the susceptibility of malignant cells to radiation will yet be found.

Other changes in the metabolism of the cancer cell have also been investigated, but do not seem so constant or significant. Changes in the blood of cancer patients have been looked for; most of these have not been of any diagnostic value because they do not appear before the growth has reached a considerable size. One of these which seems as though it may some day be of value is the Bendien or Vanadic acid test. It is based upon the fact that vanadic acid added to normal blood serum causes a precipitate, and this precipitate is increased in several diseases, one of which is cancer. Successful treatment of the cancer causes a swing back to the normal test, while reappearance of the abnormal test shows that the patient is in danger of recurrence and that treatment is necessary Like sedimentation rate of red blood cells, this test is non-specific, but when the disease is known, it seems to be able to supply a fair amount of information

Experimental Radiology

Some of the work done in the field of experimental radiology will now be considered. It is quite widely agreed that the result of radiation (X-rays and

the gamma rays of radium) is purely local on the irradiated area, and that there is no general therapeutic effect, at any rate as regards established metastases. But there is less agreement on whether this local action is a direct one on the malignant cells, or an indirect one on the stroma of the tumor. The earlier investigators mostly thought that it was a selective direct lethal action on the malignant cells. It was soon found however that not all malignant tumors were equally sensitive to the rays, and that as a rule, those tumours whose cells were dividing rapidly were the most sensitive ones. This was known to be true also of normal tissues, e.g. testis, and the growing layers of skin. The selective lethal action on malignant cells began therefore to be questioned. Furthermore, it was found that although the cells in a tissue culture could be killed by radiation, it required a dose which greatly exceeded what had been found adequate therapentically.

The curative results of radiation in any but the most rapidly-growing tumors cannot therefore be due to a direct effect on the malignant cells. Hence they have been attributed to the damaging influence of radiation on the tumor bed. Experimental work has confirmed this. For example, Cramer has shown that if a tumor in an animal is irradiated 20 minutes and then left alone, regression ensues. If however, immediately after radiation, the tumor is transplanted to another animal, it continues to grow.

The process of irradiation seems therefore to act by injuring not only the tumor cells, but also the blood vessels which supply them and the stroma in which they lie. This injury is followed by the ordinary process of repair, which is initiated by an invasion of the injured tumor by leucocytes. During the repair process the stroma overgrows and destroys those tumor cells which have been injured but not killed outright, and which would otherwise survive.

This work which suggests that the action of radiation is largely on the stroma, probably has several practical applications For example, Cramer believes that cancer cells do not become radio-resistant, and therefore he believes in low dosage over long periods, to avoid the danger of too great an injury to the powers of resistance inherent in the stroma tissues. He thinks that the rapid growth so often seen in recurrences after radiation is due to the loss of this natural resistance by the stroma, which has been injured by the previous radiation.

This work also explains why certain radio-resistant tumors, e.g. scirrhous carcinoma of breast, must be treated with caution, because sufficiently large doses to destroy all the malignant cells will be followed by radium necrosis, whereas repeated smaller doses, although they do not destroy all the malignant cells, act on the stroma and thus keep the tumor under control. Also, if the action of radiation is not even mainly a selective one on the tumor cell, then the treatment of deep-seated tumors by penetration through normal tissues must certainly have very dangerous possibilities.

Fowl Tumors

The enormous amount of work on mammalian tumors, which has been briefly reviewed in these two papers, has only served to show how very similar are normal and malignant cells. It seems evident that no definite hypothesis about the nature of the malignant process can be formulated from these studies. The evidence so far presented only indicates that the process is essentally a perverse physiological one, the understanding of which will have to await more complete knowledge of the normal physiology of the cell; that is to say, without information as to why normal cells grow in an orderly fashion and growth is stopped when certain bounds are reached, we cannot follow the lack of this property in the cancer cell.

There is only one objecton to the foregoing view that malignancy is a perverse or exaggerated physiological process, and that objection is the work on the filterable tumors of fowls. It will be remembered that mammalian tumors can be transmitted from one animal to another only by the inoculation of live tumor cells. This is not true of all avian tumors; certain tumors of fowls are transmissable not only by living cells but also by an agent separable from living cells.

Concerning the nature of these cell-free agents, there is much controversy. They have in common with the filterable viruses their ultramicroscopic size, their filterability, and their dependence upon living cells for their multiplication. But the filterable agent derived from a certain tumor will produce only tumors of that particular cell type from which it was taken, and only in that species of bird from which it was taken. On the virus theory, one would therefore have to imagine an enormous number of varieties of virus, each virus being limited in its action not only to a single species of animal, but also to a definite cell group within that species. If the theory be extended to all the different types of mammalian tumors, in all the different species of mammals, the number of varieties of virus one has to postulate becomes almost infinite.

To overcome this objection, a theory has been proposed by Gye in England, which assumes that there are *two* factors necessary for the production of a tumor. The first is a virus, which is the same for all tumor types and all species. The second is a chemical factor which varies with and is specific for each cell type and each species and it is this specific inanimate factor which decides the type of cell which is to be converted into tumor.

Much of Gye's work has not withstood criticism. Moreover, several none too plausible assumptions must be made if the virus theory is held. For instance, it must be assumed that the virus is practically ubiquitous in order to explain the artificial production of tumors at will anywhere in laboratory animals. Furthermore, there is some evidence that tar-induced tumors in fowl are transmissible by cell-free filtrates. Therefore if a virus is concerned at all in the production of these tumors, that virus must exist in the tissues of the normal bird. If this is so, then the production of tumors depends, not on the entry of a virus, but on the occurrence of local conditions which allow it to operate, and one begins to wonder why it is necessary to postulate a virus at all.

That the filterable agent is non-living is believed by Murphy of the Rockefeller Institute. He considers that the product of a malignant cell acts on an undifferentiated cell, causing it to assume the peculiar characters of the malignant cell, and in this new form the cell produces more of the agent capable of inducing the transformation of other cells. The acceptance of such a hypothesis means the acceptance of the possibility that an inanimate substance causes itself to be reproduced. He points out what seem to be other examples of this same thing in the field of bacteriology, and he gives to this group of agents the name transmissible mutagens.

The suggestions about the nature of the filterable agent therefore are that it is a living virus, a non-living agent, or, as in Gye's theory, a combination of the two.

These two papers have therefore described very briefly some of the various ways in which the nature and origin of malignant tumors is being investigated. Which of these approaches to the problem will be the most fruitful no one yet can tell.

ARISTOTLE'S INFLUENCE IN BIOLOGY

A. F. COVENTRY, B.A. (Oxon.)

Aristotle's influence in philosophy and politics and kindred subjects is generally known; his influence in biology is not so widely appreciated and is perhaps unexpected. Biology has, however, a speculative side which has so far proved insusceptible of analysis by ordinary scientific methods, a side on which Aristotle brought some of his best thinking to bear, with the result that his influence in biology is rather an aspect of his philosophical teaching than an influence of fact.

What follows is an appreciation; there is, therefore, no mention of the considerable errors that occur in Aristotle's biology; the wonder is that serious mistakes are so few in proportion to positive achievement in a field then almost unexplored; nor is there mention of the inhibiting effect his teachings had, through their very completeness of form, on less inquisitive minds in the millenium and a half after his death; this is an interesting period in the evolution of European thought, but its consideration is beyond the present purpose.

The esteem in which his works is held may be suggested by a few references to recent biological writings. E. S. Russell writes in *Form and Function*, "The *Historia animalium* is a most comprehensive work, in some ways the finest textbook of zoology ever written. Certainly few modern textbooks take such a broad and sane view of living creatures"; and again in *The Study of Living Things*, ". . . it may be questioned whether, in spite of the vast increase in our knowledge of the facts of development, we are any nearer a real understanding of it than was Aristotle, whose book, *De generation animalium*, with all its errors of detail, is still one of the fundamental treatises on the subject."

J. Needham, whose biological philosophy is very different from that of Russell, remarks in his *Chemical Embryology*, "If I have devoted a very large space to a critical discussion of Aristotle's contributions to embryology, it is, firstly, because they are actually greater in number than those of any other individual, and secondly, because they had so profound an influence upon the following twenty centuries. Embryology from the third century B.C. to the seventeenth century A.D. is meaningless unless it is studied in the light of Aristotle."

These extracts, to which others could be added, suggest that there is in Aristotle's biology matter for consideration even at this day.

Aristotle's biological thinking was based on his accumulated observations and these far exceed in number and scope any earlier collections of data. Not only does he describe about five hundred kinds of animals from all parts of the animal kingdom, but he has much to say on their functions and habits. It is impossible to do justice to his genius for observation and record by quotation, but a short passage may be of interest: "Of animals that fly some are furnished with feathered wings, as the eagle and the hawk; some are furnished with membranous wings, as the bee and the cockchafer; others are furnished with leather wings, as the flying fox and the bat. All flying creatures possessed of blood have feathered wings or leather wings; the bloodless creatures have membranous wings . . . Of creatures that can fly and are bloodless some are coleopterous or sheath-winged, for they have their wings in a sheath or shard, like the cockchafer

* From the Dept. of Biology, University of Toronto.

or the dung-beetle; others are sheathless, and of these latter some are dipterous and some tetrapterous; tetrapterous, such as are comparatively large or have stings in the tail; dipterous, such as are comparatively small or have their stings in front. The coleoptera are, without exception, devoid of stings; the diptera have the sting in front, as the fly, the horsefly, the gadfly, and the gnat." (H. A. trans. D. A. Thompson, 490a).

This passage gives a curious feeling of intimacy, which is characteristic of much of Aristotle's biological writing; it suggests, very tantalizingly, that he could have written much more on the subject if he had wanted—perhaps the lecture-note theory of his works may explain this. Here, too, is shown an example of one of Aristotle's most important contributions to the method of biology, that of comparison. The comparative method is the foundation of an understanding of organic structure and function, and he was one of the first to apply it to a wide range of material; it may be illustrated by another extract: "Almost all sanguineous animals have a gall-bladder. In some this is attached to the liver, in others separated from that organ and attached to the intestines, being apparently in the latter case no less than in the former an appendage of the lower stomach (i.e., opening into the intestine beyond the stomach). It is in fishes that this is most clearly seen. For all fishes have a gall-bladder; in most of them it is attached to the intestine, being in some, as in the Amia, united with this, like a border, along its whole length. It is similarly placed in most serpents . . . In some animals there is absolutely no gall bladder at all—in the horse, for instance, the mule, the ass, the deer, and the roe; and in others, as the camel, there is no distinct bladder, but merely small vessels of a biliary character. Again there is no such organ in the seal, nor, of purely sea-animals, in the dolphin. Even within the limits of the same genus, some animals appear to have and others to be without it. Such, for instance, is the case with mice; such also with man. The same has occurred with sheep and goats." (P. A. trans. Ogle 676b). Here is knowledge, the greatness of which, in spite of a few errors, may be judged by comparison with any current comparative anatomy of similar scope; and this passage does not at all exhaust what Aristotle has to say on the subject, for in the *Historia animalium* he discusses the same organ and adds many other forms to those mentioned here.

The application of the comparative method led Aristotle to an important principle, now called the Principle of Unity within a Class. Everyone knows in a general way what is meant by a bird or a mammal; perhaps what is meant by a vertebrate; Aristotle gave precision to such popularly known groups (his *genera*), and defined others, in virtue of his discovery that in each there is a common plan underlying the superficial diversity of structure. This idea is pervasive in his work, and in Darwinian biology it became one of the strongest props of evolutionary doctrine.

Accumulated data and discoveries of method and principle naturally led Aristotle, typically Greek in his passion for order, to devise a classification, and the opening chapter of the *De partibus animalium* discusses the possible bases; habits, methods of locomotion, food, structure, methods of reproduction; he uses the last. He rejects as inapplicable to his material the continuous use of the dichotomy, and he ultimately arrives at the first natural classification of animals. True, in his extant works he nowhere exposes it in tabular form, but it is not hard to reconstruct his views—views that dominated all attempts to classify till the work of Linnaeus in the middle of the eighteenth century. Whitehead writes: "The logical instrument which Aristotle used for the analysis of actual facts into more abstract ele-

ments was that of classification into species and genera. This instrument has its overwhelmingly important application for science in its preparatory stages." (Science and the Modern World, p. 244).

In a more purely theoretical field he established clearly the idea of a Scale of Nature. "Nature proceeds little by little from things lifeless to animal life in such a way that it is impossible to determine the exact line of demarcation, nor on which side thereof an intermediate form should lie. Thus next after lifeless things in the upward scale comes the plant, and of plants one will differ from another as to its amount of apparent vitality; and, in a word, the whole genus of plants, whilst it is devoid of life as compared with animals, is endowed with life as compared with other corporeal entities. Indeed, as we just remarked, there is observed in plants a continuous scale of ascent towards the animal . . . In regard to sensibility, some animals give no indication whatsoever of it, whilst others indicate it but indistinctly . . . And so throughout the entire animal scale there is a graduated differentiation in amount of vitality and in capacity for motion." (H. A. 588b).

This idea persisted strongly until the first half of the nineteenth century, when it was superseded by the idea of a number of branches.

The problems of development and inheritance have intrigued human curiosity since earliest times, and it was inevitable that Aristotle, in company with his contemporaries and forerunners, should turn his attention to them. The remarkable thing is that in spite of the handicap imposed by the lack of technical equipment "Aristotle should have produced, apparently without effort, a text-book of embryology of essentially the same type as Graham Kerr's or Balfour's . . . The depth of Aristotle's insight into the generation of animals has not been surpassed by any subsequent embryologist." (Needham).

In this textbook, *De generatione animalium,* Aristotle first among biologists stated clearly the idea of embryonic recapitulation. The passage reads: "That they (animal embryos) possess the nutritive soul is plain. As they develop they also acquire the sensitive soul in virtue of which an animal is an animal. For the end is developed last, and the peculiar character of the species is the end of the generation of each individual." 736a). In other words, higher animals pass in their development through series of stages that become less and less general in character till the particular individual is attained; a striking anticipation of a theory on which in recent biology great, though various, emphasis has been laid.

Early embryologists were much exercised over the problem whether the patent increase of complexity during development is in fact a progressive differentiation from an initial simplicity, or whether it is merely an enlargement and an unfolding of complexity already present in miniature in the undeveloped germinal material; the problem of epigenesis versus preformation. William Harvey is generally credited with the first clear statement of the epigenetic point of view, but Cole remarks (*Early Theories of Sexual Generation,* p. 132), "It is impossible to read Aristotle's account of the development of the chick without realizing that Harvey adopted the idea direct from his authority."

Believing, then, in a real epigenesis, Aristotle was faced with the two great questions: firstly, the problem of inheritance; secondly, what controls the orderly course of differentiation with the production of form?

His treatment of the first is a brilliant example of his analytical powers, for he defines clearly the alternatives about which discussion of to-day revolves; these are sometimes called the atomistic and holistic point of view.

The first holds that offspring resemble parents because the body is a sort of mosaic of point to point resemblance, the additive effect of which is to produce a whole that resembles the parent; the second supposes that there is a general resemblance of the bodies as a whole, which involves more or less close secondary resemblances between the component parts. For modern biologists the matter is still unsettled; Aristotle concluded on grounds that he gives at some length that the second accords best with the facts as he knew them. His genetic views are closely connected with what he taught of the origin of germinal material; for him this was the semen, the really vital element in reproduction, since the female contributed only matter in which the activity of the semen could organize form. In spite of the important error of this view, he reaches a substantially correct view of the principle involved. He disposes on logical grounds of the current view—derived from the Hippocratics and Democritus—that the semen is put together of particulate samples from every region of the body and concludes that what must be looked for in the semen is some sort of organizing or moulding power.

For Aristotle, as clearly as for the biologist of to-day, the central problem is that of form, and his attempt to give a casual account of what being alive involves is largely an attempt to account for the development of form and for the apparent purposiveness of development.

Aristotle states, perhaps as self-evident, that "nature always seeks an end" or "everything exists for a final cause." The final, and at the same time the formal, cause of a living organism is its abstract idea; the material cause is the stuff out of which it is made; the efficient cause is motion controlled, perhaps produced, by a soul; this is an immaterial functional activity of the living organism, in general terms entelechy, prior in thought though subsequent in time to the body.

This activity is form as opposed to the formless potentiality of matter; working on the matter by means of motion it ensures the development of characteristic structure and properties. Since for Aristotle there are well-marked grades of organic complexity, of functional activity, he postulates three main souls, nutritive, sensitive and rational.

The nutritive and sensitive souls are inseparable from the body, are indeed in some fashion the product of living matter; organisms live by possession of a nutritive soul, and this is the only soul of plants and of early embryos of animals. During development animals become distinguished from plants by acquiring a sensitive or perceptive soul, in virtue of which they are more fully responsive to their surroundings. Man has a rational soul; this is not the product of matter, but comes from outside and is possessed of divinity.

Aristotle thus holds that for each organism according to its estate there is a non-physical factor guiding it towards its predetermined goal; only in man has this factor any degree of autonomous existence apart from the body. This system is complete and formally satisfying.

Biologists of to-day are still searching for an explanation of vital processes. The great success that has followed the application of the experimental methods of chemistry and physics to vital phenomena has led many to hope for a complete description of these phenomena in chemical and physical terms; others find the complexity of life make this hope impossible. It is the old antithesis between materialism and vitalism, between 'man a machine' and 'man not a machine' and those who hold the latter view find in Aristotle's teaching a complete vitalistic doctrine, requiring only some modification to bring it into accord with recent discoveries. Driesch, the leader of modern vitalists, borrows freely from

this source, and indeed takes for the name of his "autonomous or vitalistic factor" the name entelechy, admittedly somewhat changing its meaning, since Aristotle's entelechy was not necessarily autonomous.

It is in this borderland where science and philosophy overlap that Aristotle's influence is most active. One school of thought still draws immediately on his formal teaching; the other, disbelieving in final causes in nature and so unable to accept his solution of their problems, can none the less admire him as the founder of scientific biology and a great figure among those Greeks who bequeathed to their successors the scientific spirit that has made rational knowledge of the world possible.

ABSTRACTS FROM CURRENT LITERATURE

The Diagnosis of Hepatic Disorders.
Duncan Graham, C.M.A.J., 1935, **33.** 247.

"Recent studies on the use of liver function tests in different hepatic disorders have shown quite definitely that these tests are of little value in the early diagnosis of chronic hepatic disease. One must still rely on the clinical history and the physical examination of the patient to provide evidence for the diagnosis and for the determination of the clinical cause."

The determination of the size of the liver by physical examination is of great importance. Conditions causing enlargement of the liver may be divided into two main groups; (1) enlargement with visible jaundice; (2) enlargement without visible jaundice. The differential diagnosis of jaundice, acording to McNee's classification is discussed. The significance of an associated enlargement of the spleen is pointed out.

The commonest causes of enlargement of the liver without jaundice are venous congestion from cardiac failure, secondary malignant disease of the liver, and portal cirrhosis.

The chief causes of diminution in size of the liver are: acute and subacute necrosis of the liver; the atrophic form of portal cirrhosis; and obstruction of the hepatic bile duct.

Professor Graham's papers on clinical diagnosis are of the greatest interest to students because they present material which simply cannot be obtained from text books. Three other papers of a similar type, by Prof. Graham, have appeared in the Canadian Medical Association Journal in recent years. These are:—

Clinical Diagnosis of Arteriosclerosis and and Hypertension. C.M.A.J., 1935, **32,** 29.

Focal Infection, C.M.A.J., 1931, **25,** 422.

Differential Diagnosis of Superficial Glandular Swellings. C.M.A.J., 1930, **22,** 324.

On the Administration of Iron.
G. H. W. Lucas and V. E. Henderson, C.M.A.J., 1936, **34,** 53.

The hypochromic anaemias are divided into (1) The nutritional anaemia of young children. (2) Chlorosis, which has now disappeared and (3) idiopathic, hypochromic anaemia. All these anaemias respond well to adequate doses of iron. The evidence is presented for the view that iron is only absorbed when present in the intestine in the ferrous state. The need for giving adequate doses is emphasized. Many proprietary iron preparations contain ridiculously small amounts of iron. It is very difficult to give sufficient iron by intra-muscular injection. Iron is best administered in the form of one of the iron containing mixtures of the Canadian Formulary or as reduced iron in powders or cachets. A very interesting observation upon the increase in the iron content of vegetables when cooked in an iron pot is recorded. The increase ranges from 10 to 40 times the amount of iron originally present in the vegetables.

This paper is only one of many which Prof. Henderson and his colleagues, in the Pharmacology Department and elsewhere, have published in the Canadian Medical Association Journal in recent years. These articles are extremely practical and supply information that cannot be found elsewhere in such readily available form. Every student should read them in his fourth year and many of them are worth re-reading in the fifth and sixth years for their clinical applications.

The articles referred to will be found in the Canadian Medical Association Journal as follows. Volume 23, pages 226, 551, 673 and 818. Volume 24, pages 77, 262, 412, 541, 684 and 833. Volume 25, page 63. Volume 28, pages 298 and 497. Volume 29, pages 22, 430 and 663. Volume 32, pages 538, 554, 579 and 645. Volume 33, pages 64, 176 and 303.

LEAD POISONING IN THE AUTOMOBILE INDUSTRY

By ALASTAIR MACDONALD, '37.

PART I: EXPOSURE TO AND ABSORPTION OF LEAD; CLINICAL PICTURE AND TREATMENT.

The lead hazard in the automobile industry has been described recently by an authority on Industrial Hygiene as the greatest industrial "lead problem" that he has yet seen. With advances in automobile design instituted within the past few years, the amount of lead used has increased tremendously. No manufacturer of automobile bodies is able to avoid the lead problem to-day because of the demand for "all-steel" bodies. While it is true that some manufacturers are able to minimize the hazard through the nature of the design of their product, the prevailing condition is universal and has demanded immediate attention by each individual concern.

Nature of the Lead Exposure.

The seat of exposure in this industry lies in the production of the automobile bodies. The present-day "all steel" body is composed of several large stampings which are welded together. At the seams so formed, there is a variable amount of irregularity and roughness to the surface. This is covered up by plastering the whole area with copious quantities of solder. In order to round out the body contour and give a smooth finish, this solder is ground down carefully and rounded off to conform with the body lines. Until recently, most of this operation was carried out by a process known as "disc-sanding," in which the workman used a machine similar to a hard drill, to the end of which was fitted a fibre disc impregnated with carborundum, about 8 inches in diameter. This machine turned at high speed and rapidly smoothed out the surface of the soldered area. Since the disc was pliable, it could be used to great advantage on curved surfaces, under door jambs, etc., so that it was very efficient from a manufacturing viewpoint. Unfortunately, however, this process was very detrimental to the health of the men working at and in the vicinity of the "disc-sanding," for lead dust was scattered in large quantities for considerable distances in all directions. Not only the men who were actually engaged in the operation, but those at distances up to 50 to 75 feet were breathing a relatively high concentration of dust. The actual hazard was not as great as might be presumed, due to the fact that the coarseness of the lead particles caused them to settle out fairly rapidly. Nevertheless, the concentration of dust in the air was sufficient to produce the signs of lead absorption in some of the men in the vicinity.

The seriousness of the condition was not realized in most instances until the first cases of plumbism appeared about one year ago. Precautions against the hazard were then taken by equipping the men with respirators of various types. The best and cheapest type was found to be a flat pad-like affair which fitted close to the nose and mouth. The pads are composed of layers of gauze and absorbent cotton, used in any thickness desired. It was supposed at first that this type would not be very satisfactory because fine particles travelling at high velocity and aided by the inspiratory effort of the men might be well expected to penetrate the mask.

This occurs if the mask is much less than one quarter inch thick. If thicker than this, the men object to them and discard them because they interfere with breathing and become uncomfortable. This is the type of respirator which supplanted the "bag" type, a closely woven cotton bag about 6 inches deep, fitting closely around the mouth and nose. The latter was an excellent respirator except for the fact that every time a man finished his operation on one body and was waiting for the next, he would pull off his mask and leave it hanging around his neck. Since the air was full of dust, the sinking particles would fall into the open mouthpiece of the bag during that interval, so that when he replaced his mask to recommence work, the workman would inhale fair quantities of lead dust with his first breath.

It is difficult for the average individual to appreciate how hard it is to get the men to wear their masks all the time, especially those not actually engaged in the disc-sanding operations. Masks are tiresome nuisances when they must be worn more or less continuously for 8 hours a day, especially in hot weather. Therefore, it was decided to suspend all disc-sanding and buffing operations on solder except where it could not be avoided. The work is now done with very coarse files which roll the solder up into large shavings and drop them onto the floor. Since 12 to 20 linear feet of soldered seaming per body could be done in this way, leaving only 3 to 4 feet to be done by disc-sanding, the greater part of the hazard is eliminated. As a further precaution, it has been suggested that the remaining disc-sanding be done in a booth with forced draught ventilation. When this is done, only a very few men actually engaged in disc-sanding will have to wear masks and be in any position to absorb lead, and even they will be fairly safe. It would also eliminate the necessity of having all the men in the department examined periodically for evidence of lead absorption, as is now done, thereby eliminating considerable expense to the automobile firms.

Absorption of Lead.

Such is the condition which exists in the automobile industry to-day and more particularly, as seen by the author while in the employ of the Medical Department of one of the large Canadian firms during 1935. Some companies have much more "footage" of lead work to contend with than this particular firm, so that in these cases, the lead problem reached rather alarming heights. Some of the body manufacturers made it a rule that all employees who came into contact with lead were allowed extra time for lunch in order that they might wash properly before eating. In the past most authorities have maintained that the greater part of the absorption took place through the alimentary canal. In the instance under discussion, this does not seem to be the case, the absorption seeming to be of a respiratory nature, as it is rather difficult to see how sufficient quantities of lead could be swallowed from inhaled dust to give rise to such rapidly developing cases of acute plumbism. Absorption through the skin does not play an appreciable part here either, for the only exposed surfaces are the face and hands and, occasionally, the arms. There seems to be little absorption of metallic lead in the latter manner, for all cases of plumbism were found in areas where the dust concentration was highest.

One of the striking features was the relative sensitivity to lead displayed by the exposed men. Of 250 men employed in the body-build department of a certain factory, probably only half were in areas where the dust concentration was high enough to cause concern. Of this number, only about 75 were in areas of relatively high concentration, and, in these there were found 3 clinical cases and about 10 showed definite evidence of lead absorption of such degree that clinical plumbism would have resulted. Some men working very close to the disc-sanding op-

eration showed little or no absorption, whereas others working 30 to 75 feet away were demonstrated to be absorbing lead in fair quantities. Apparently, the former group were able to excrete rapidly their daily lead intake, for they have never shown any clinical evidence of lead absorption at any time.

Clinical Picture.

A brief review of the clinical picture of plumbism will assist the reader in visualizing the treatment of the condition. Usually, there is not a rapid onset of symptoms, the patient being caused little concern until the condition has advanced to the point where he cannot carry out his daily tasks adequately. In adults, a mild gastro-intestinal upset is the first warning of the approaching trouble. It is in the nature of a dyspepsia, vague transitory abdominal pains increasing to those of acute colic. When the symptoms are developed the cramps are exceedingly severe and, in some cases, are referred to the chest. Either constipation or diarrhoea may be present. There is loss of appetite, generalized weakness, and a feeling of fatigue, the patient complaining of "always feeling tired." This tiredness and lethargy are most marked in the middle of the morning as a rule. These symptoms are found in both the acute and chronic forms of plumbism. In the acute form there is an accompanying anaemia which may be moderately severe, whereas in the chronic form it is less marked.

One of the remarkable features of the syndrome is the development of stippling in the red blood cells, which may reach rather high numbers in severe cases. When this sign accompanies a history of gastro-intestinal disturbance, one may fairly safely diagnose the condition as one of plumbism. In the more advanced stages of the disease, various forms of neuritis are seen. The upper limb is most frequently attacked but if exposure persists, the lower limbs and muscles of the trunk may be involved. The typical wristdrop of lead poisoning is not seen in the acute forms of the disease, as a rule, but rather in the chronic form where there has been prolonged exposure and steady absorption. Paralysis occurs only in the more severe cases, there being one instance on record where every muscle below the neck was paralysed.

The lead line on the gums has long been held up as a diagnostic point but it seems that it seldom occurs apart from dirty mouths. Consequently, it is not seen as frequently today as in the past. One must examine a suspected lead line very carefully to be sure that it is in the gums and not on the teeth or due to foreign material lodged about the teeth or gums. This line is a dull blue-black colour and is said to be due to the deposition of sulphides of lead in the dental margins of the gum tissue. It seems to appear more frequently in the upper than in the lower gums.

Headache and depression are frequently encountered and in some cases, even hysteria. Lead encephalitis is occasionally met with, especially in children.

In all cases where palsy is not encountered a physical examination reveals nothing, and in some cases palsy may be the sole finding. The urine may or may not show lead, but the test is exacting and cumbersome and it is the experience of many that it is valueless. Examination of the faeces is of even less value as most of the lead detected has not been absorbed, so that even lead excretion is not being determined.

The blood picture is the most constantly reliable finding. Stippling of red cells in amounts over 5,000 per million is diagnostic of lead absorption. No other condition except benzol poisoning, perhaps, produces such a blood picture; even the end stages of pernicious anaemia do not produce this degree of stippling. One may make the bald statement that the absolute diagnosis of plumbism cannot be made without the examination of a blood smear for stippled cells. Smears

should be taken on several successive days for there is often considerable daily variation in the stipple count. If values over 5,000 stippled cells per million are found at any time, the patient should be removed from his exposure and treatment instituted.

Treatment

The treatment is both symptomatic and specific. To relieve the colic, atropine or belladonna may be given in full doses and in severe cases, intravenous calcium chloride has been administered. Morphia may be required in some cases. Where palsies have occurred, massage and electrical treatment of the affected part are indicated. In acute lead poisoning it is deemed advisable to hold the lead in the bones until the acute features have subsided. The lead is transported in the body as lead phosphate. Excess calcium absorption favours the harmless storage of lead in the bones, while a calcium deficiency favours excretion of lead. Therefore, in acute plumbism a high calcium diet is prescribed, two quarts of milk daily being required. After a month or so when the acute features have subsided, the procedure is reversed, a low calcium diet being given. This assists the natural deleading process of the body greatly. The length of time of deleading depends upon the amount of lead absorbed and the individual's ability to excrete it. When lead is stored in the bones to any extent it is usually demonstrable by X-ray plates, a clear-cut line of deposited lead being seen in the areas of greatest vascularity, e. g. about the epiphyseal line of the long bones.

Prevention of Lead Absorption

Although the therapeutic treatment of plumbism is very satisfactory, since the majority of cases occur in adults exposed to lead by their occupation, the best treatment is obviously prevention. Every precaution should be taken to prevent absorption of lead by exposed workers. Cleanliness with its proper provision should be insisted upon. Respirators must be worn where lead dust is prevalent. All workers who are exposed should have frequent medical examinations, particularly an examination of the blood smear for stippling.

In the factory in which the author was employed the following procedure was carried out. It was taken for granted that all men in the body-build department either were exposed or had been exposed to lead at some time. The disc-sanding operation was reduced to the minimum and all men in the vicinity of this operation were equipped with respirators of the type previously described. Every man in the department was given a blood smear examination which was repeated at suitable intervals. All men who showed high stippled cell counts, whether manifesting symptoms or not, were removed from exposure by giving them work in other departments where there was no exposure. At the same time they were placed on high calcium diets and weekly examination of the blood smears done. After about one month their diet was changed to a low calcium one. When their stippled cell counts had maintained a normal level over a period of a few weeks they were returned to their original work. In this manner, a thorough and effective check on the lead problem was maintained. With the reduction of the disc-sanding operation it was noted that there was a strong tendency to lowered stippled cell counts throughout the whole group and the number of men with high counts was greatly reduced.

End of Part I

Part II will consist of the technique and interpretation of the blood smear examination. It will apear in the next issue.

BOOK REVIEW

FIFTY YEARS A SURGEON, ROBERT T. MORRIS, M.D. E. P. Dutton & Co. $4.00.

To the student of Medicine a well-written medical autobiography is always of great interest. Perhaps this is because the student's especial training gives him a better understanding of the Doctor's actions, perhaps because he is able to leave for a time the daily grind of acquiring information for an hour at a lecture, then another lecture, or a lab. or a clinic, from nine to five each day for six years, and be present for a brief time in the profession for which he is euipping himself. It has been this reviewer's pleasure to enjoy the simplicity of Axel Munthe's "Story of San Michele," Halliday Sutherland's vigorous adventures in his "Arches of the Years," Bland Sutton's egotistical existence in his "Story of a Surgeon," and now the story of a brilliant surgeon, who after more than fifty years of active practice is still young and enthusiastic.

Robert T. Morris graduated in 1882, entering the world of surgery at a transitional period. His reminiscences contain an absorbing blend of information and entertainment. Perhaps I can illustrate his vivid style by actually quoting one or two paragraphs from an early chapter of his book.

"In hospital work the operator often threw off his coat and rolled up his sleeves in a most daring and carefree way but that sort of thing would not do at all for operation in a polite private home in the presence of a husband and terrified family—where most of the surgery was done in that day. In order to avoid soiling his clothes the operator often put on a kitchen apron, preferably of some subdued colour or a linen duster. When a visitor dropped in with a lighted cigar in his hand he was warned to keep away from the anaesthetic if ether was being used because of the danger of an explosion. The visitor almost always remembered these instructions unless he became absent-minded when the operation developed interesting features. Such explosions occurred now and then in different hospitals, but not twice in any of them. Flies did not worry an operator at all because they were certain to go to the wound and leave him alone."

One of the most interesting sections of the book is that of the Fourth Era of Surgery and evidently this subject lies very close to Dr. Morris' heart. He describes the Heroic Era in which period operators worked rapidly without

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knowledge of anatomy, the Anatomical Era ushered in by Vesalius and first practised by John Hunter and his pupils in which a refined knowledge of anatomy was needed by the surgeon, the Pathologic Era founded on the work of Lister and Pasteur in which the microbe became bigger than man and finally the Physiologic or Fourth Era of Surgery based on the discoveries of Metchnikoff in which man's abilities to handle microbes is realized provided that he is not hampered by large operation wounds, prolonged operations or extensive drainage operations. Dr. Morris caused somewhat of a furor in 1896 when his mortality from unselected cases of appendicitis was 2% while that of other surgeons was 15-30%. Since that time Dr. Morris has been preaching his doctrine of "get in and get out" with as little operative interference as possible. Incidently Dr. Morris considers it criminal to operate on an adherent appendix wearing gloves, as without gloves, using touch, a smaller operation wound is sufficient, the whole proceedure is quicker and less handling of viscera is necessary.

Fifty Years a Surgeon is a book by a brilliant American Surgeon who has retained a refreshing originality of thought, who has the ability to criticize fetish, and who is fortunately gifted with a forceful style of expression. His book contains much of interest to the doctor and student, much that is controversial that will provoke thought and revision of acepted ideas, and much that is human and enjoyable.

—D. G. H. M.

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